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TI Generation of CD8+ T cell lines with specific cytotoxicity for autologous Chronic Lymphocytic Leukemia B cells.
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AB Although a lot of effort has been put in the expansion of autologous CD8+ T cells in response to CD40L activated Chronic Lymphocytic Leukemia (CLL)-B cells both by our group and by others (Blood 93:1992, 1999), the responding T cells are mainly CD4+. Experiments with normal donors show that normal CD8+ T cells can proliferate in response to CD40L activated CLLB (CD40L-CLLB) cells. Both our group (unpublished data) and others (Blood 95:999, 2000) have shown that CpG-motif containing phosphorothioate oligonucleotides (CpG-ODN) activate CLLB cells to express co-stimulatory molecules and that it is synergystically with CD40L activation. CpG-ODN also activates dendritic cells. Based upon this we investigated if CpG-ODN could promote long term proliferation of autologous CD8+ T cells in response to CD40L-CLLB cells. For this purpose PBMC's of CLLB patients were cultured with or without CpG-ODN (**TGACTGTGAACGTTCGAGATGA**) or non-CpG-ODN (TGACTGTGAAGGTTAGAGATGA or TGACTGTGAATGTTAGAGATGA). Initial anergy of the T cells was overcome by a onetime stimulation with immobilized mAb's to CD3 (OKT3) and CD28 (TN228), for subsequent stimulation CD40L-CLLB cells were added every 3 days. The cultures were followed over at least 4 weeks, including their T cell receptor (TCR) repertoire. By week 3 the cultures with CpG-ODN showed on average (n=5) a double amount of CD8+ T cells compared to the controls or the cultures with the non-CpG-ODN. The T cell cultures got more restricted to certain Vbeta TCR, showing that they got more oligoclonal. The involvement of dendritic cells was shown in a depletion experiment: the effect of CpG-ODN could be completely abolished by removing all adherent cells. The cultures in the presence of adherent cells and CpG-ODN showed about a 3 fold increase in the production of IFNgamma and IL-6 compared to either CpG-ODN or co-culture with adherent cells alone. With CpG-ODN we were able to show CD1a+ cells in CLL-PBMC's after 4 days in culture, whereas none were detected in the absence of CpG-ODN. These CD1a+ dendritic cells were phenotyped by FACS (CD40+, CD86+, CD4+, CD54 +++, HLA-DR+++). Cytotoxicity (CTL) assays with the purified CD8+ T cells showed that these cells caused about 50% of the autologous CD40L-CLLB cells to undergo apoptosis at a effector to target ratio (E/T) of 10:1. This killing could be inhibited by

W6/32, a mAb specific for a non-polymorphic epitope of HLA class I, and by mAb's specific for the Vbeta TCR which was increasing in response to co-culture with autologous CD40L-CLLB cells. Leading to the conclusion that CpG-ODN is capable of stimulating long term proliferation of CD8+ T cells with high potency to kill autologous CLLB cells via a TCR restricted manner.